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EDITOR'S COMMENTARY

Naturing and nurturing the competent oocyte: it's all in the niche

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Despite claims to the contrary, and the currency it carries in human ARTs, harvesting more eggs in the course of infertility treatment is not necessarily a good thing when it comes to truly meaningful outcomes. The "more is better" mentality may have been successfully circumvented in the case of azoospermia, but not so for Mother Nature's design for monovular species like ourselves. The challenge in human ARTs of obtaining oocytes of the *competent* variety remains alive and well if any hope of generating embryos obtains for transfers resulting in a term (or near-term) pregnancy.

A decade has passed since Swain and Pool pointed the finger at the oocyte when it came to proffering explanations for fertilization failures, already set in the backdrop of ICSI and its widespread adoption [1]. And decades of research in animal models firmly established the challenges involved with getting an oocyte to grow up and mature, forecasting oogenesis to be the rate-limiting step in producing female gametes capable of making embryos that had the "right stuff."

In this month's issue, we take a journey from the inner reaches of the niche within which oocytes undergo their growth and maturation, to an examination of overdue technologies just finding their way into the realm of reproductive medicine. We begin with the review by Navarro and colleagues (*Influence of follicular fluid and cumulus cells on oocyte quality: clinical implications*), followed by considerations for the introduction of platelet-rich-plasma (PRP) into the realm of reproductive medicine by Bos-Mikich (*Platelet-rich plasma therapy and reproductive medicine*) and potential applications articulated by Aghajanova and colleagues (*In vitro evidence that platelet-rich plasma stimulates cellular processes involved in endometrial regeneration; Platelet-rich plasma in the management of Asherman syndrome: case report*).

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The oocytes' acquisition of competencies itself entails much more of a marathon rather than a sprint! For many years, the long-sought-after "competent" oocyte was viewed as more the byproduct of a magical mystery tour through a niche known as ovarian follicle than some experimentally tractable biological process. In humans, the best guess is the mystery tour takes some months to occur–at least for those women lucky enough to have the ovarian functionality consistent with child bearing.

That this magical mystery tour has taken on the glamour and distinction accorded royalty at center stage becomes the purview of many a dreamer hoping to see a future where making an oocyte will become a matter of stem cell and bioengineering feats for those in need of a competent oocyte (or wishing to sell them). Somewhere between fact and fancy is envisioned a tidy little process bioengineered or imagined to become the future egg factory by evading or reiterating the "natural" ovarian process that thus far has escaped definition in rigorous terms.

So just how complicated might building an egg factory be? A recent review by Conti and Franciosi spells out for the first time in unparalleled detail some of the molecular signatures embedded in what appears to be an encyclopedic dictum for making eggs [2]. And following this recipe (more of a litany of contingencies) might come longawaited answers to what went wrong, or right, when those few oocytes used in ARTs either failed or succeeded to make a baby. Among the many signatures for the document known as "oogenesis" comes an array of molecular modifications that even in the final hours-the maturation stage of oogenesis when final preparations for fertilization and preimplantation development take place-enable RNA dynamics that could not have been forecasted before the age of modern molecular biology was applied to model organisms [2]. So here is a rendering of the requisite orchestration within the oocytes' cytoplasm, driving erasure of the meiotic mannerisms of an oocyte to those of a somewhat casual, almost adolescent phenotype, reluctantly adopting just a few of the rules governing zygotic mitoses to get the embryogenesis show on the road.

As might have been anticipated with the discovery of a wide world of new RNAs, attending the emergence of so many species of functional RNAs (emphasizing how obsolete the Watson-Crick landscape is fast becoming), defining roles for RNAs along the pathway of oogenesis has become a central challenge. Besides traditional motifs tied to linear translation, long non-coding RNAs (LNCs) [3, 4] now stand as crucial to the readouts at protein or gene expression levels marking stepping stones for egg production. Herein it seems lies much of the information writing the script for embryogenesis well beyond implantation! Good luck to those purveyors of embryo quality assessment. From the "timelapsers" to "chromosome counters" obsessed with bits and pieces of a DNA-based information reservoir, it is looking more and more like epigenetics and other types of imprints were deposited long ago in the follicular niche designated to make a competent oocyte.

Uncovering the roots of oocyte competencies requires a retrospective look back at the classical mammalian oocyte literature. Competencies were first defined as the ability of a follicular oocyte to reinitiate meiosis (GVBD) and progress to metaphase of meiosis-2 in culture. With time it was learned that both fertilization and subsequent development were attributes acquired by intrafollicular oocytes at specific stages of oogenesis as reflected by oocyte size, age and stage of the reproductive cycle and/or culture conditions. In fact, it was this line of investigation that opened the gateway to the field of in vitro maturation (IVM) for human ARTs, and as reviewed in these pages launched Bob Edwards' career efforts following a brief and productive sabbatical with the Joneses at Johns Hopkins back in the 1960s. One final historical note pertains to the use of IVM to delineate the biochemical mechanisms at play during the meiotic to mitotic cell cycle switch occurring during the transformation of the oocyte into the zygote—a Nobel prize winning effort from yesteryear!

The clinical imperative for adoption of IVM looms large despite many efforts to bring it to fruition as a routine ART. Two important papers in this issue highlight both the state of affairs in protocol development (*The effect of short-term exposure of cumulus-oocyte complexes to in vitro maturation medium on yield of mature oocytes and usable embryos in stimulated cycles*) and the growing need to optimize IVM in the field of fertility preservation (*Outcome of immature oocyte collection of 119 cancer patients during ovarian tissue harvesting for fertility preservation*).

From IVM studies like these, the importance of maintaining somatic cells as a life support system for oocytes has only served to reinforce how critical granulosa cells are throughout the life history of female gametes [4]. And looking towards the future, it becomes clear that tinkering with the native state of granulosa cell–oocyte interactions seems to negatively influence both the growth and final stages of oocyte maturation whether such insults derive from iatrogenic interventions or those found during the natural processes of ovarian aging or disease conditions like PCOS. Towards this end, the Follicle Biology Unit led by Johan Smitz in Brussels has been making notable strides in refining and applying IVM clinically [5]. Efforts like this emphasize the importance of recapitulating the niche within the Graafian follicle as a whole or within the specialized cumulus-oocyte complex under *ex vivo* conditions given what has become appreciated regarding the role of bidirectional communication at the oocyte-soma interface [6].

As knowledge of the Watson-Crick model for regulating gene expression assumes more the character of planned obsolescence in an evolution-designed landscape dominated by chromatin complexity, genomes, gene editing and the like, a note of caution is in order when reconsidering how nature and nurture conspire in the central process of oogenesis. With evidence growing for genetic self-engineering of cells in a changing environment, our reliance on classical genetics in reproductive medicine is beginning to resemble more of a myopic condition instead of a eutopia that may someday yield oocytes fabricated within an *ex vivo* niche [7]. Only time will tell whether narrow-sighted approaches for reeling in the red herring improve the practice and safety of ARTs while the world of RNAs and "omics" wait in line to underwrite future research with true promise of clinical application.

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